AMENDMENTS TO THE CLAIMS

Claims 1 **(Withdrawn)** A method for *in vivo* down-regulation of growth differentiation factor 8 (GDF-8) activity in an animal, including a human being, the method comprising effecting presentation to the animal's immune system of an immunogenically effective amount of at least one GDF-8 analogue wherein is introduced at least one modification in the GDF-8 amino acid sequence which has as results that

- immunization of the animal with the analogue induces production of antibodies against the GDF-8 polypeptide, and
- a substantial fraction of GDF-8 B-cell epitopes are preserved, and
- a foreign T helper epitope (T_H epitope) is introduced corresponding to any one of residues 18-41, 49-69, or 79-104 in SEQ ID NO: 11 or 12 by means of addition, deletion, insertion or substitution, or introduced corresponding to an equivalent sequence from a GDF-8 polypeptide of different origin than human, bovine, porcine, chicken or turkey, or a foreign T_H epitope is inserted or substituted into any one of the loop areas or the flexible termini in the GDF-8 polypeptide.

Claims 2-52 **(CANCELLED)**

53. **(Previously Presented)** A method for *in vivo* down-regulation of growth differentiation factor 8 (GDF-8) activity in an animal, including a human being, the method comprising effecting presentation to the animal's immune system of an immunogenically effective amount of at least one GDF-8 analogue wherein is introduced at least one modification in the GDF-8 amino acid sequence which has as results that

- immunization of the animal with the analogue induces production of antibodies against the GDF-8 polypeptide, and
- a substantial fraction of GDF-8 B-cell epitopes are preserved, and
- a foreign T helper epitope (T_H epitope) is introduced corresponding to any one of residues 18-41, 49-69, or 79-104 in SEQ ID NO: 11 or 12 by means of addition, deletion, insertion or substitution, or introduced corresponding to an equivalent sequence from a

GDF-8 polypeptide of different origin than human, bovine, porcine, chicken or turkey, or a foreign T_H epitope is inserted or substituted into any one of the loop areas or the flexible termini in the GDF-8 polypeptide.

54. **(Withdrawn)** The method according to claim 53, which further comprises that

- at least one first moiety is introduced which effects targeting of the modified molecule to an antigen presenting cell (APC) or a B-lymphocyte, and/or
- at least one second moiety is introduced which stimulates the immune system, and/or
- at least one third moiety is introduced which optimises presentation of the modified GDF-8 polypeptide to the immune system.

55. **(Withdrawn)** The method according to claim 54, wherein the modification includes introduction as side groups, by covalent or non-covalent binding to suitable chemical groups in GDF-8 or a subsequence thereof, of the foreign T_H epitope and/or of the first and/or of the second and/or of the third moiety.

56. **(Withdrawn)** The method according to claim 54, wherein the modification includes amino acid substitution and/or deletion and/or insertion and/or addition.

57. **(Withdrawn)** The method according to claim 56, wherein the modification results in the provision of a fusion polypeptide.

58. **(Withdrawn)**The method according to claim 56, wherein introduction of the amino acid substitution and/or deletion and/or insertion and/or addition results in a substantial preservation of the overall tertiary structure of GDF-8.

59. **(Withdrawn)** The method according to claim 54, wherein the modification includes duplication of at least one GDF-8 B-cell epitope and/or introduction of a hapten.

60. **(Withdrawn)** The method according to claim 55, wherein the foreign T_H epitope is immunodominant in the animal.

61. **(Withdrawn)** The method according to claim 54, wherein the foreign T_H epitope is promiscuous, such as a natural promiscuous T_H epitope and an artificial MHC-II binding peptide sequence.

62. **(Withdrawn)** The method according to claim 61, wherein the natural T_H epitope is selected from a Tetanus toxoid epitope such as P2 or P30, a diphtheria toxoid epitope, an influenza virus hemagluttinin epitope, and a *P. falciparum* CS epitope.

63. **(Withdrawn)** The method according to claim 54, wherein the first moiety is a substantially specific binding partner for a B-lymphocyte specific surface antigen or for an APC specific surface antigen, such as a hapten or a carbohydrate for which there is a receptor on the B-lymphocyte or the APC, such as mannan or mannose.

64. **(Withdrawn)** The method according to claim 54, wherein the second moiety is selected from a cytokine, a hormone, and a heat-shock protein.

65. **(Withdrawn)** The method according to claim 64, wherein the cytokine is selected from, or is an effective part of, interferon γ (IFN-γ), Flt3L, interleukin 1 (IL-1), interleukin 2 (IL-2), interleukin 4 (IL-4), interleukin 6 (IL-6), interleukin 12 (IL-12), interleukin 13 (IL-13), interleukin 15 (IL-15), and granulocyte-macrophage colony stimulating factor (GM-CSF), and wherein the heat-shock protein is selected from the group consisting of HSP70, HSP90, HSC70, GRP94, and calreticulin (CRT), or an effective part thereof.

66. **(Withdrawn)** The method according to claim 54, wherein the third moiety is of lipid nature, such as a palmitoyl group, a myristyl group, a farnesyl group, a geranyl-geranyl group, a GPI-anchor, and an N-acyl diglyceride group.

67. **(Withdrawn)** The method according to claim 53, wherein the GDF-8 analogue is derived from the C-terminal, active form of GDF-8, such as an analogue derived from a bovine, porcine, human, chicken, sheep, or turkey GDF-8 polypeptide.

68. **(Withdrawn)** The method according to claim 67, wherein the GDF-8 polypeptide has been modified by substituting at least one amino acid sequence in SEQ ID NO: 11 or 12 with at least one amino acid sequence of equal or different length which contains a foreign T_{II} epitope, wherein substituted amino acid sequences are comprised in residues 1-12, 18-41, 43-48, 49-69, or 79-104 in SEQ ID NO: 11 or 12, or wherein the GDF-8 polypeptide has been modified by

inserting at least one amino acid sequence which contains a foreign T_H epitope, wherein insertion is performed anywhere in positions 1-12, 18-30, 42-51, 82-86, and 105-109 in SEQ ID NO: 11 or 12.

69. **(Withdrawn)** The method according to claim 53, wherein presentation to the immune system is effected by having at least two copies of the GDF-8 analogue covalently or non-covalently linked to a carrier molecule capable of effecting presentation of multiple copies of antigenic determinants.

70. **(Withdrawn)** The method according to claim 53, wherein an effective amount of the GDF-8 analogue is administered to the animal via a route selected from the parenteral route such as the intradermal, the subdermal, the intracutaneous, the subcutaneous, and the intramuscular routes; the peritoneal route; thc oral route; the buccal route; the sublinqual route; the epidural route; the spinal route; the anal route; and the intracranial route.

71. **(Withdrawn)** The method according to claim 70, wherein the effective amount is between 0.5 μg and 2,000 μg of the GDF-8 polypeptide, the subsequence thereof or the analogue thereof.

72. **(Withdrawn)** The method according to claim 71, which includes at least one administration of the GDF-8 analogue per year, such as at least 2, at least 3, at least 4, at least 6, and at least 12 administrations per year.

73. **(Withdrawn)** The method according to claim 70, wherein the GDF-8 analogue optionally has been formulated with a pharmaceutically and immunologically acceptable carrier and/or vehicle and has been formulated with an adjuvant which facilitates breaking of autotolerance to autoantigens, such as an adjuvant selected from the group consisting of an immune targeting adjuvant; an immune modulating adjuvant such as a toxin, a cytokine and a mycobacterial derivative; an oil formulation; a polymer; a micelle forming adjuvant; a saponin; an immunostimulating complex matrix (an ISCOM matrix); a particle; DDA; aluminium adjuvants; DNA adjuvants; γ-inulin; and an encapsulating adjuvant.

74. **(Withdrawn)** The method according to claim 71, wherein the GDF-8 analogue is contained in a virtual lymph node (VLN) device.

75. **(Withdrawn)** The method according to claim 53, wherein presentation of the GDF-8 analogue to the immune system is effected by introducing nucleic acid(s) encoding the GDF-8 analogue into the animal's cells and thereby obtaining *in vivo* expression by the cells of the nucleic acid(s) introduced.

76. **(Withdrawn)** The method according to claim 75, wherein the nucleic acid(s) introduced is/are selected from naked DNA, DNA formulated with charged or uncharged lipids, DNA formulated in liposomes, DNA included in a viral vector, DNA formulated with a transfection-facilitating protein or polypeptide, DNA formulated with a targeting protein or polypeptide, DNA formulated with calcium precipitating agents, DNA coupled to an inert carrier molecule, DNA formulated with chitin or chitosan, and DNA formulated with an adjuvant.

77. **(Withdrawn)** The method according to claim 75, wherein the nucleic acids are administered intraarterially, intravenously, or by the routes defined in claim 18.

78. **(Withdrawn)** The method according to claim 76, wherein the nucleic acid(s) is/are contained in a VLN device and/or is/are formulated as defined in claim 21.

79. **(Withdrawn)** The method according to claim 76, which includes at least one administration of the nucleic acids per year, such as at least 2, at least 3, at least 4, at least 6, and at least 12 administrations per year.

80. **(Withdrawn)** A method for increasing the muscle mass of an animal, the method comprising down-regulating GDF-8 activity according to the method of claim 53 to such an extent that the muscle mass is increased at least 5% when compared to animals which exhibit normal GDF-8 activity, such as at least 10, 15, 20, 25, 30, 35, 40, and 45%.

81. **(Currently Amended)** A GDF-8 analogue ~~derived from an animal~~comprising a GDF-8 polypeptide that has been modified by means of at least one modification that comprises substituting ~~at least one~~ a first amino acid sequence in SEQ ID NO: 11 or 12 with ~~at~~ a ~~least one~~ second amino acid sequence which comprises a foreign T_H epitope, wherein said first amino acid sequence is from one or more of residues 1-12, 18-41, 43-48, 49-69 or 79-104 in SEQ ID NO: 11 or 12, or that has been modified by inserting at least one amino acid sequence which comprises a foreign T_H epitope at one or more of residues 1-12, 18-30, 42-51, 82-86 and 105-109 in SEQ ID NO: 11 or 12.

82. **(Previously Presented)** An immunogenic composition comprising an immunologically effective amount of a DGF-8 analogue according to claim 81, the composition further comprising a pharmaceutically and immunologically acceptable carrier and/or vehicle and optionally an adjuvant.

83. **(Previously Presented)** An immunogenic composition according to claim 82, wherein the adjuvant is selected from the group consisting of the adjuvants of claim 73.

84. **(Withdrawn)** A nucleic acid fragment which encodes a GDF-8 analogue according to claim 81.

85. **(Withdrawn)** A vector carrying the nucleic acid fragment according to claim 84, such as a vector capable of autonomous replication.

86. **(Withdrawn)** The vector according to claim 85 which is selected from the group consisting of a plasmid, a phage, a cosmid, a mini-chromosome, and a virus.

87. **(Withdrawn)** The vector according to claim 85, comprising, in the 5'→3' direction and in operable linkage, a promoter for driving expression of the nucleic acid fragment according to claim 84, optionally a nucleic acid sequence encoding a leader peptide enabling secretion of or integration into the membrane of the polypeptide fragment, the nucleic acid fragment according to claim 84, and optionally a terminator.

88. **(Withdrawn)** The vector according to claim 85 which, when introduced into a host cell, is either capable of being integrated in the host cell genome or which is not capable of being integrated in the host cell genome.

89. **(Withdrawn)** The vector according to claim 85, wherein the promoter drives expression in a eukaryotic cell or drives expression in a prokaryotic cell.

90. **(Withdrawn)** A transformed cell carrying the vector of claim 85.

91. **(Withdrawn)** The transformed cell according to claim 90, which is capable of replicating the nucleic acid fragment according to claim 84.

92. **(Withdrawn)** The transformed cell according to claim 90, which is a micro-organism selected from a bacterium, such as a bacterium of the genus *Escherichia* (preferably *E. coli*), *Bacillus*, *Salmonella*, or *Mycobacterium* (preferably a non-pathogenic *Mycobacterium* cell such as *M. bovis* BCG), a yeast, a protozoan, or a cell derived from a multicellular organism selected from a fungus, an insect cell such as an S_2 or an SF cell, a plant cell, and a mammalian cell.

93. **(Withdrawn)** The transformed cell according to claim 90, which expresses the nucleic acid fragment according to claim 84.

94. **(Withdrawn)** The transformed cell according to claim 93, which secretes or carries on its surface, the GDF-8 analogue according to claim 81.

95. **(Withdrawn)** The method according to claim 53, wherein presentation to the immune system is effected by administering a non-pathogenic micro-organism or virus which is carrying a nucleic acid fragment which encodes and expresses the GDF-8 polypeptide or analogue.

96. **(Withdrawn)** The method according to claim 95, wherein the virus is a non-virulent pox virus.

97. **(Withdrawn)** The method according to claim 96, wherein the virus is a vaccinia virus or the bacterium is one as defined in claim 92.

98. **(Withdrawn)** The method according to claim 95, wherein the non-pathogenic micro-organism or virus is administered one single time to the animal.

99. **(Withdrawn)** A composition for inducing production of antibodies against GDF-8, the composition comprising

- a nucleic acid fragment according to claim 84 or a vector according to claim 85, and
- a pharmaceutically and immunologically acceptable carrier and/or vehicle and/or adjuvant.

100. **(Withdrawn)** The composition according to claim 99, wherein the nucleic acid fragment is formulated according to claim 76.

101. **(Withdrawn)** A stable cell line which carries the vector according to claim 85 and which expresses the nucleic acid fragment according to claim 84, and which optionally secretes or carries the GDF-8 analogue according to claim 81 on its surface.

102. **(Withdrawn)** A method for the preparation of the cell according to claim 90, the method comprising transforming a host cell with the nucleic acid fragment according to claim 84 or with the vector according to claim 85.

103. **(Currently Amended)** A GDF-8 analogue ~~derived from an animal~~comprising a GDF-8 polypeptide that has been modified by means of at least one modification that comprises substituting ~~at least one~~a first amino acid sequence in SEQ ID NO: 12 with ~~at least one~~a second amino acid sequence which comprises a foreign T_H epitope, wherein said first amino acid sequence is from one or more of residues 1-12, 18-41, 43-48, 49-69 or 79-104 in SEQ ID NO: 12 or that has been modified by inserting at least one amino acid sequence which comprises a foreign T_H epitpe at one or more of residues 1-12,18-30, 42-51, 82-86, and 105-109 in SEQ ID NO:12 .

104. **(Previously Presented)** The GDF-8 analogue according to claim 103, wherein the modification is made in residues 18-41 of SEQ ID NO: 12.

105. **(NEW)** A GDF-8 analogue comprising a GDF-8 polypeptide that has been modified by at least one modification selected from the group consisting of

- substituting a first amino acid sequence in SEQ ID NO: 11 or 12 with a second amino acid sequence which comprises a foreign T_H epitope, wherein said first amino acid sequence is from one or more of residues 1-12, 18-41, 43-48, 49-69 or 79-104 in SEQ ID NO: 11 or 12;
- inserting at least one amino acid which comprises a foreign T_H epitope at one or more of residues 1-12, 18-30, 42-51, 82-86 or 105-109 in SEQ ID NO: 11 or 12,

- adding an amino acid sequence which comprises a foreign T_H epitope at the N- or C-terminus to SEQ ID NO: 11 or 12;

-substituting a first amino acid sequence in SEQ ID NO: 11 or 12 with a second amino acid sequence which comprises a foreign TH epitope, wherein said first amino acid sequence is a loop area or a flexible terminus in the GDF-8 polypeptide comprising SEQ ID NO:11 or 12; and

- inserting at least one amino acid sequence which comprises a foreign T_H epitope into a loop areas or in a flexible terminus in the GDF-8 polypeptide comprising SEQ ID NO: 11 or 12;

wherein the number of amino acid additions, insertions, deletions, and substitutions does not exceed 60.

106. **(NEW)** The method according to claim 105, wherein the foreign T_H epitope is introduced by means of insertion.

107. **(NEW)** The method according to claim 105, wherein the foreign T_H epitope is introduced by means of addition.

108. **(NEW)** The method according to claim 105, wherein the foreign T_H epitope is introduced by means of substitution.

109. **(NEW)** The method according to claim 105, wherein the foreign T_H epitope is promiscuous.

110. **(NEW)** An immunogenic composition comprising an immunologically effective amount of a GDF-8 analogue according to claim 105, the composition further comprising a pharmaceutically and immunologically acceptable carrier and/or vehicle and optionally an adjuvant.